Steatotic liver disease

Mads Israelsen, Sven Francque, Emmanuel A Tsochatzis, Aleksander Krag

Steatotic liver disease is the overarching term for conditions characterised by abnormal lipid accumulation in the liver (liver or hepatic steatosis). Steatotic liver disease encompasses what was previously termed non-alcoholic fatty liver disease (NAFLD), which is now called metabolic dysfunction-associated steatotic liver disease (MASLD). Additionally, steatotic liver disease includes alcohol-related liver disease (ALD) and MetALD, the new classification for the overlap between MASLD and ALD, and rare causes of liver steatosis. Cirrhosis is globally the 11th leading cause of death, and steatotic liver disease has become the leading cause of cirrhosis in the EU and USA. Steatotic liver disease affects around 30% of the global population and is mainly driven by obesity, type 2 diabetes, and alcohol intake, but only a minor proportion with steatotic liver disease progress to cirrhosis. The presence and progression of liver fibrosis led by hepatic inflammation is the main predictor of liver-related death across the entire spectrum of steatotic liver diseases. A combination of recent advancements of widely available biomarkers for early detection of liver fibrosis together with considerable advancements in therapeutic interventions offer the possibility to reduce morbidity and mortality in patients with steatotic liver disease. This Seminar covers the recent reclassification of steatotic liver disease and how it reflects clinical practice and prognosis. For early detection of liver fibrosis, we propose a collaborative diagnostic framework between primary care and liver specialists. Lastly, we discuss current best practices for managing steatotic liver disease, we explore therapeutic targets across the spectrum of steatotic liver diseases, and we review the pipeline of drugs in development for MASLD.

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Centre for Liver Research and Department of Gastroenterology and Hepatology, Odense University Hospital, Odense, Denmark (M Israelsen PhD, Prof A Krag PhD)**; Institute of Clinical Research, Faculty of Health Sciences, University of Southern Denmark, Odense, Denmark** (M Israelsen, Prof A Krag)**; Department of Gastroenterology and Hepatology, Antwerp University Hospital, Antwerp, Belgium** (Prof S Francque PhD)**; Laboratory of Experimental Medicine and Paediatrics, Faculty of Medicine and Health Sciences** (Prof S Francque) **and InflaMed Centre of Excellence, Translational Sciences in Inflammation and Immunology, University of Antwerp, Antwerp, Belgium** (Prof S Francque)**; UCL Institute for Liver and Digestive Health, Royal Free Hospital, University College of London, London, UK** (Prof E A Tsochatzis PhD)

Correspondence to: Professor Aleksander Krag, Centre for Liver Research and Department of Gastroenterology and Hepatology, Odense University Hospital, 5000 Odense C, Denmark **Aleksander.Krag@rsyd.dk**

Introduction

In this Seminar we address the recent reclassification and new nomenclature of fatty liver disease as steatotic liver disease, encompassing what was formerly known as non-alcoholic fatty liver disease (NAFLD)—and its subtype non-alcoholic steatohepatitis (NASH)—and alcohol-related liver disease (ALD), and other rare causes of liver steatosis.[1] This reclassification and new nomenclature, initiated by several regional liver societies, has resulted from a large multi-stakeholder consensus-driven process following a strict methodology and now has global endorsement from more than 75 societies.[2] Importantly, this shift integrates steatotic liver disease within a spectrum encompassing ALD and recognises the potential coexistence of factors that synergistically drive disease progression. Given that more than 30% of the global population has liver steatosis,[3,4] and that in most countries a large proportion of these populations concurrently consume alcohol (with 5–15% engaging in harmful alcohol consumption),[5,6] these figures underline the far reaching implications of this reclassification for clinical practice. The new framework, acknowledging both cardiometabolic risk factors (CMRFs) and alcohol consumption, is of crucial importance for various medical fields, including primary care, internal medicine, hepatology, gastroenterology, endocrinology, and obesity medicine. Reclassification also holds substantial importance for public health and health-care systems.[7] Furthermore, the steatotic liver disease framework facilitates the conceptualisation of steatotic liver disease subclasses as a dynamic and overlapping spectrum allowing for the integration of diagnostic and management recommendations across these subclasses. This Seminar builds on this new approach and integrates the evidence across steatotic liver disease subclasses.

While liver steatosis is a common feature in many liver diseases, most cases are associated with alcohol consumption and CMRFs, particularly type 2 diabetes and overweight, or a combination of these.[1] The group of less common causes of liver steatosis are distinct and are not the focus of this Seminar. The naming of this condition as steatotic liver disease underscores liver steatosis as a central feature. However, it is well recognised that liver inflammation and fibrosis are the key clinical targets due to their association with disease severity and prognosis (panel 1).[11–13]

Epidemiology of steatotic liver disease

The predominant risk factors for steatotic liver disease include obesity, insulin resistance, and alcohol consumption. WHO estimates that in 2022, 43% of all individuals 18 years and older were overweight (BMI >25 kg/m²) and 16% were living with obesity (BMI >30 kg/m²). In 2021, there were 529 million (95% uncertainty interval [UI] 500–564) people living

Search strategy and selection criteria

We searched the Cochrane Library, MEDLINE, and EMBASE all from inception to January, 2024. We used the search terms: "steatotic liver disease" or "fatty liver disease" or "non-alcoholic liver disease" or "non-alcoholic steatohepatitis" or "alcohol related/associated liver disease" or "alcoholic liver disease" alone and in combination with the terms "fibrosis" or "biomarker". We selected publications from the last 5 years, but did not exclude commonly referenced and highly regarded older publications. We also searched the reference lists of articles identified and selected those we judged to be relevant. Review articles are cited to provide readers with more details and more references than this Seminar has room for.

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Panel 1: Liver steatosis and chronic liver disease

Liver steatosis is defined as the accumulation of lipids in liver parenchymal cells. Alcohol intake has long been recognised as a cause of liver steatosis, yet there are reports of cases of liver steatosis in people not consuming alcohol that date from the 19th century, and some of these reports even already linked the disease to obesity and diabetes.[8] In 1980, Ludwig and colleagues described a series of patients with liver steatosis not consuming alcohol and proposed the term non-alcoholic fatty liver disease (NAFLD) so as to oppose it to the well-known cause of alcohol intake.[9] Since then, NAFLD has been linked to metabolic dysfunction characterised mainly by obesity and diabetes.[10] NAFLD was redefined in 2023 and integrated in the spectrum of steatotic liver disease based on a global consensus process and is now endorsed by more than 75 societies across the world. The clinical significance of liver steatosis remains debated; however, the factors that contribute to steatosis (obesity, diabetes, and alcohol) can also trigger hepatic inflammation and fibrosis. Over time, progression of liver fibrosis can lead to cirrhosis and its complications associated with significant mortality. Therefore, the detection of liver fibrosis, rather than steatosis, is the cornerstone of most initiatives aimed at identifying, intervening in, and preventing symptomatic steatotic liver disease.

Panel 2: Global prevalence of risk factors for steatotic liver disease

- 43% have overweight
- 16% live with obesity
- 6% live with type 2 diabetes
- 50% consume alcohol regularly
- 20% drink heavily at least once a month
- 16% engage in harmful alcohol consumption
- 25% carry genetic risk alleles in *PNPLA3*

with diabetes, and the global age-standardised total diabetes prevalence was 6·1% (95% UI 5·8–6·5).[14]

More than half of the entire global population reports regular alcohol use[15] with 1·03 billion (95% UI 0·85–1·19) males (35·1%, 95% UI 29·1–40·7, age 15 years and older) and 312 million (95% UI 199–432) females (10·5%, 95% UI 6·72–14·6, age 15 years and older) engaging in harmful alcohol consumption.[16] Over the past decades, there has been a noticeable increase in the prevalence of these risk factors, a trend projected to persist[15] and this increase is mirrored in the rising prevalence of liver steatosis, liver fibrosis, and cirrhosis.[3,6,17–19]

Currently, 33% (ranging from 25% in Western Europe to 44% in Latin America) of the global population has steatotic liver disease with considerable regional differences attributed to disparities in lifestyle, dietary habits, and alcohol intake.[3,19] It is anticipated that most individuals with liver steatosis are related to CMRFs, but studies have reported that 58% under-report alcohol intake when being assessed for liver disease,[20] and 12–30% with heavy alcohol intake are not classified as ALD due to underreporting.[21,22]

Cirrhosis is globally the 11th leading cause of death, the second in Europe for years of working life lost, with 2–4% of all deaths attributed to cirrhosis.[6,23,24] There are several genetic single nucleotide polymorphisms that increase the risk of developing cirrhosis in individuals with steatotic liver disease. Among these, the best described are genetic risk alleles in PNPLA3, particularly the rs738409 variant.[25] These alleles are carried by approximately 20–25% of the world's population, with prevalences ranging from 10–75% in different populations.[26] There is significant evidence that this genetic variation is associated with increased susceptibility to liver steatosis, fibrosis, and cirrhosis.[25] The combined increase of alcohol consumption and CMRFs, particularly type 2 diabetes and overweight, has become the leading cause of cirrhosis in the EU and the USA,[24,27] and is projected to be the same in Asia following the expected reduction of viral hepatitis B and C (panel 2).[28]

Reclassification of steatotic liver disease

Since the first description of NAFLD,[9] it became clear that the disease was linked to what is currently known as the components of the metabolic syndrome, in particular overweight or obesity, insulin resistance, prediabetes and diabetes, and dyslipidaemia.[10] It was rapidly acknowledged that the term non-alcohol fatty liver disease did not reflect this cause of the disease, and the fact that the exclusionary definition of NAFLD did not allow to accurately describe chronic liver disease in the context of combined metabolic and alcohol-related factors, but the nomenclature remained unchanged.

In 2020, Elslam and colleagues proposed a new name and definition, with a positive criteria of metabolic dysfunction-associated fatty liver disease (MAFLD) when steatosis was detected in the presence of metabolic alterations.[29] The proposal was an attempt to solve the problems, but had inherent limitations, most notably the fact that it allowed for co-existing disease drivers to be present without appropriately acknowledging their roles contributively and separately. Also, there is increasing evidence on the role of stigma associated with the term fatty in some cultures.[30] Lastly, the MAFLD proposal did not result from a rigorous consensus process.[31]

Recently, a large consensus process involving a wide and comprehensive range of stakeholders and following a stringent methodology issued a new framework of terminology and definitions to settle the issues.[1] First, the term fatty was replaced by steatotic to avoid stigma. The old term NAFLD referring to liver steatosis in the context of CMRFs is now named metabolic dysfunction associated steatotic liver disease (MASLD). Second, the

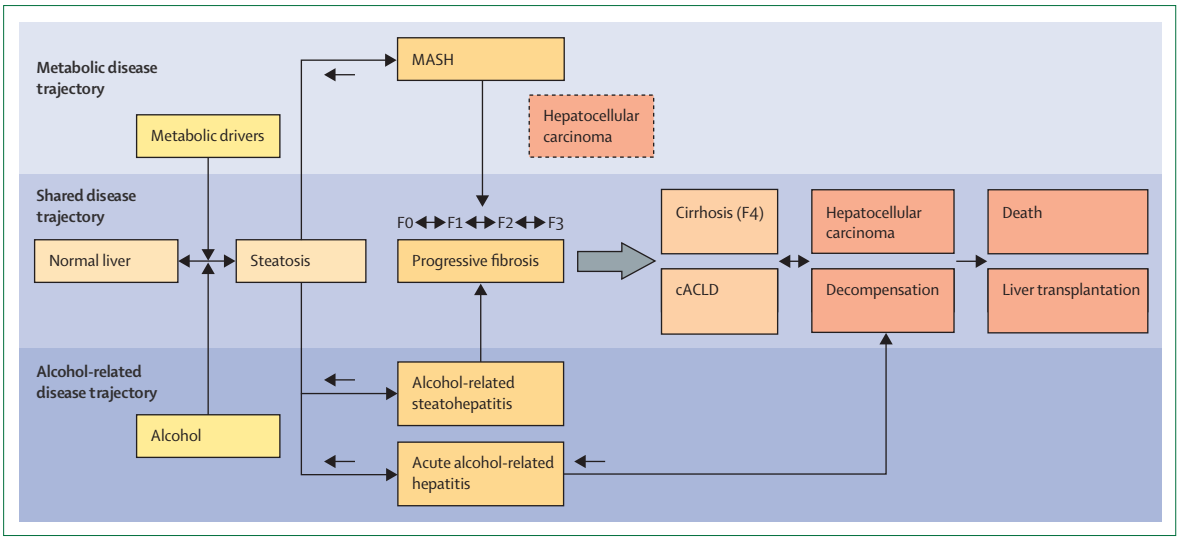

***Figure 1*: The natural history of steatotic liver disease**
In MASLD only, starting from a normal liver and depending on the balance between metabolo-inflammatory drivers and defence mechanisms, steatosis will be accompanied by steatohepatitis, which can result in progressive fibrosis ultimately leading to cirrhosis and the complications.[32,33] Given the disease continuum and some intrahepatic heterogeneity, the concept of cACLD might better reflect the transition from advanced fibrosis (F3) to cirrhosis (F4), as this is a gradual shift in severity. Hepatocellular carcinoma can develop at any stage, although the risk is probably the highest in the cirrhotic stage and ill-defined in earlier stages.[34] At any stage, disease regression is possible pending improvements in the cardiometabolic milieu. Alcohol exposure induces steatosis and various degrees of hepatocyte damage depending on several risk factors.[35] Continuous exposure in susceptible people will lead to progressive fibrosis, the pattern of which might be somewhat different from MASLD, but uses the same staging system. Episodes of acute severe alcohol-related hepatitis can accelerate disease progression or even lead by itself to liver decompensation. The occurrence of hepatocellular carcinoma is usually restricted to the cirrhotic stage. The natural history of people combining risk factors for MASLD and alcohol consumption is ill-defined, but they might reinforce each other with an accelerated disease course and an increased risk of complications. cACLD=compensated advanced chronic liver disease. MASH=metabolic dysfunction-associated steatohepatitis. MASLD=metabolic dysfunction-associated steatotic liver disease.

new nomenclature introduced the overarching concept of steatotic liver disease, hence the starting point of diagnosis being the feature of steatosis, regardless of the aetiology. This concept deliberately favours a broad differential diagnosis, stressing the potential co-existence of multiple risk factors of liver steatosis, thus supporting a holistic care. Under the steatotic liver disease umbrella, there are subcategories of all potential causes of liver steatosis, with alcohol and metabolic dysfunction being the two leading aetiologies. MASLD and ALD share several central pathophysiological features starting with liver steatosis that can be accompanied by hepatic inflammation (steatohepatitis), which is considered the driver of liver fibrosis and ultimately leads to cirrhosis with complications (figure 1).[32,33] Furthermore, both conditions share common genetic risk factors including single nucleotide polymorphisms in *PNPLA3*, *TM6SF2*, and *HSD17B13*.[36–38] Historically, MASLD and ALD have been regarded as distinct entities, but in clinical practice many individuals have risk factors for both conditions and this overlap adversely affects prognosis.[39,40]

Steatotic liver disease subcategories are based on the presence of at least one CMRF and the level of alcohol consumption (figure 2). Individuals with steatotic liver disease and at least one CMRF and alcohol consumption less than 20–30 g per day are classified as having MASLD. Individuals with steatotic liver disease and both at least one CMRF and alcohol consumption more than 20–30 g per day but less than 50–60 g per day are classified as having MetALD and bridges the gap between MASLD and ALD (figure 2).[42] If alcohol consumption exceeds 50–60 g per day, the diagnosis is ALD, although the contribution of CMRFs to disease progression is also important in these individuals.[40,43,44] Individuals without CMRFs but with alcohol consumption more than 20–30 g per day are also labelled ALD.

Subclassification not only mirrors the clinical phenotype of steatotic liver disease more accurately, but also provides positive criteria for each subclass enabling targeted clinical trials. In this framework, people combining different risk factors for steatotic liver disease and chronic liver disease can be appropriately diagnosed and managed for all contributing factors. The new framework did not change the concepts of steatohepatitis (only changing NASH to metabolic dysfunction-associated steatohepatitis [MASH]) nor the liver fibrosis staging, which along with the large overlap between NAFLD and MASLD, also implies that the scientific data gathered so far with the old nomenclature are still valid.[45,46]

A particular diagnostic challenge is posed in patients who exhibit liver fibrosis, but without any diagnostic modality showing steatosis and in whom the presence or history of CMRFs or alcohol consumption are the only aetiological clues. Alcohol-induced steatosis typically resolves with abstinence from drinking, which is why many patients with a history of excessive alcohol

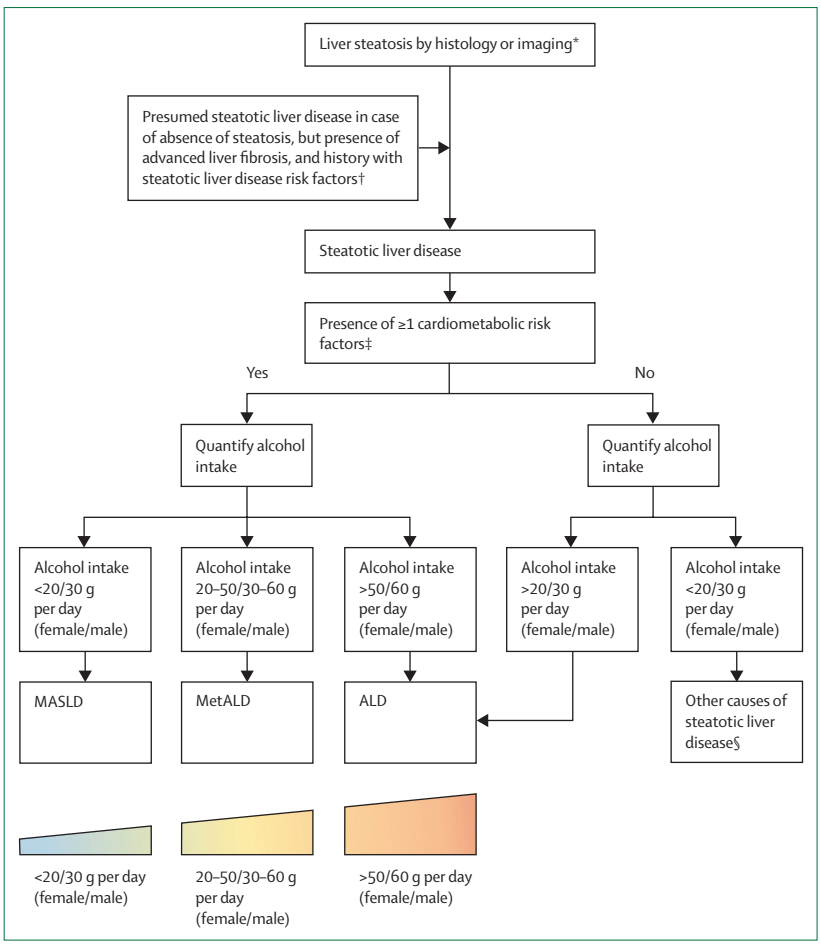

Figure 2: **Flowchart showing classification and subclassification of steatotic liver disease**
Classification based on the diagnostic criteria for steatotic liver disease nomenclature as established by the multi-society Delphi consensus statement in 2023.[1] ALD=alcohol-related liver disease. MASLD=metabolic dysfunction-associated steatotic liver disease. MetALD=metabolic dysfunction and alcohol-related liver disease. *Liver steatosis is defined histologically as the presence of lipid vacuoles in 5% and more of hepatocytes.[41] Imaging including standard ultrasound and MRI-proton density fat fraction can be used as non-invasive assessments for steatosis. †Absence of steatosis can be observed if steatotic liver disease risk factors are eliminated or reduced, or when extensive liver fibrosis is predominant in some cases of severe cirrhosis. However, other lesions, particularly fibrosis, are less dynamic and can persist. In cases of fibrosis without steatosis, a history of previous steatotic liver disease risk factors could justify a diagnosis of presumed steatotic liver disease, which includes cases with histologically confirmed advanced fibrosis (stages F3 and F4), or a corresponding liver stiffness measurement (transient elastography >12 kPa). In these cases, other causes of chronic liver disease should be carefully considered. ‡The criteria for cardiometabolic risk factors used in the definition of steatotic liver disease: (1) BMI of ≥25 kg/m^2 (adjusted based on ethnicity), or a waist circumference ≥80 cm for women and ≥94 cm for men; (2) fasting serum glucose levels of ≥5·6 mmol/L (100 mg/dL), 2-hour post-load glucose concentrations of ≥7·8 mmol/L (140 mg/dL), glycated haemoglobin of ≥5·7% (39 mmol/mol), presence of type 2 diabetes, or treatment for type 2 diabetes; (3) blood pressure of ≥130/85 mm Hg, or the use of specific antihypertensive drugs; (4) plasma triglycerides of ≥1·70 mmol/L (150 mg/dL), or undergoing lipid-lowering treatment; and (5) plasma HDL-cholesterol levels of ≤1·3 mmol/L (40 mg/dL) for women and ≤1·0 mmol/L (50 mg/dL) for men, or receiving lipid-lowering treatment. §Drug-induced liver injury, monogenic diseases (eg, lysosomal acid lipase deficiency), Wilson's disease, hypobetalipoproteinaemia, inborn errors of metabolism, and miscellaneous liver disease (eg, genotype 3 hepatitis C virus infection, malnutrition, celiac disease, and HIV infection).

intake do not present with steatosis when undergoing assessment for liver disease.[47] Furthermore, features of steatosis and steatohepatitis tend to disappear in steatotic liver disease when cirrhosis progresses.[48] Therefore, steatosis is not mandatory for the diagnosis of MASLD or MASH with advanced fibrosis or cirrhosis,[1] which also applies to patients with MetALD and ALD with significant fibrosis.[1] In these cases, excluding other relevant aetiologies is key (panel 3).

Panel 3: **Changes in terminology to reduce stigma**

- Fatty liver disease changed to steatotic liver disease (SLD)
- Non-alcoholic fatty liver disease (NAFLD) changed to metabolic dysfunction-associated steatotic liver disease (MASLD)
- Non-alcoholic steatohepatitis (NASH) changed to metabolic dysfunction-associated steatohepatitis (MASH)
- Metabolic and alcohol-related liver disease (MetALD) newly defined
- Alcoholic liver disease (ALD) changed to alcohol-related liver disease (ALD)
- Alcoholic cirrhosis changed to alcohol-related cirrhosis
- Alcoholic changed to person with alcohol-use disorder (AUD)
- Alcoholic hepatitis (AH) changed to alcohol-related or alcohol-associated hepatitis (AH)
- Alcoholism changed to alcohol-use disorder (AUD)

Clinical presentation of steatotic liver disease

Steatotic liver disease is mostly asymptomatic in the pre-cirrhotic stages, as is the case with most causes of chronic liver disease.[49] Typically, patients present either with incidentally discovered abnormal liver blood tests or with a steatotic liver on an ultrasound, most commonly performed for another indication. Of the incident cases of cirrhosis, 70% are first diagnosed on an acute admission with hepatic decompensation.[17] Symptoms such as dull right upper quadrant pain or fatigue are non-specific, but might affect quality of life.[50] Patients with MASLD are usually overweight or obese and might have additional features of the metabolic syndrome, such as type 2 diabetes, dyslipidaemia, or arterial hypertension. The diagnosis of an alcohol problem is best made from the patient history, but can be hindered by under-reporting. Therefore, alcohol consumption biomarkers can be useful to help reveal and quantify recent alcohol intake.[51] There is a higher prevalence of patients with steatotic liver disease among individuals with low socioeconomic status, who are at an increased risk of developing advanced liver disease.[52,53] Once cirrhosis develops, patients can exhibit spider naevi, palmar erythema, splenomegaly, or experience muscle cramps. Decompensated cirrhosis presents with ascites, hepatic encephalopathy, or variceal bleeding.[49] Hepatocellular cancer is a complication of cirrhosis in steatotic liver disease, but can also present in patients without cirrhosis in MASLD.[54] Laboratory findings can include increased levels of transaminases, however, patients can have persistently normal liver enzyme levels, even with advanced fibrosis or cirrhosis.[55] An aspartate aminotransferase level higher than alanine aminotransferase level can indicate either the presence of

cirrhosis or alcohol as the main driver of steatotic liver disease. Hyperferritinaemia with normal transferrin saturation is a common finding and does not indicate the need for venesections, but can be associated with an increased risk of liver related events.[56] Patients with ALD might exhibit macrocytosis due to the long-term toxic effects of alcohol on the bone marrow.[57]

Diagnostic approach

Steatosis

Steatotic liver disease is usually diagnosed by ultrasound, which is often performed for an unrelated indication. Ultrasound is not particularly sensitive as it can be negative when steatosis is less than 20% and is operator-dependent.[58] MRI-proton density fat fraction is considered the non-invasive gold standard for imaging, but is only available in specialist centres and is currently used predominantly in the context of clinical trials.[59] Laboratory-based scores (eg, the fatty liver index) can be used in population studies.[59] The controlled attenuation parameter (CAP) value as part of liver assessment by Fibroscan, has emerged as an alternative way for assessing steatosis, but needs further validation, requires specific equipment, and is not widely available in non-hepatology settings.[60]

Aetiology

Steatotic liver disease is an umbrella term, therefore the diagnosis of liver steatosis should trigger a comprehensive investigation of all potential causes.[1] The presence of abnormal liver blood tests should lead to a screen for all potential causes of liver disease, even in the presence of obvious causes such as increased alcohol intake or cardiometabolic comorbidities.[49] Specifically for liver steatosis, the three most common causes (ie, alcohol, metabolic dysfunction, and drug-induced liver injury) should be looked for, whereas the search for more rare causes should be triggered if the findings cannot be explained or are disproportionate to the degree of alcohol intake or CMRFs.

The distinction between MASLD, MetALD, and ALD is not always straightforward as it is mainly based on clinical history and self-reported alcohol consumption.[21] Accurate assessment of alcohol history is paramount for the proper classification of individuals with steatotic liver disease.[31] However, self-reported alcohol consumption is frequently under-reported, leading to diagnostic misclassification. A retrospective study of 279 patient diagnosed with chronic liver disease showed that 161 (57·7%) of 279 patients under-reported alcohol consumption compared with phosphatidylethanol levels.[20] In a study of 184 consecutive patients with steatotic liver disease, 32 (28·6%) of 112 patients with presumed MASLD had moderate to excessive ethanol consumption based on hair ethylglucuronide testing.[22] Similarly, a register-based study from Sweden of 15 107 patients diagnosed with MASLD found 2630 (17·4%) patients to have a previous or later diagnosis of an alcohol-related illness.[21] These particular patients had considerably poorer prognosis than patients with only MASLD, underlying the clinical significance of a correct diagnosis.[21,47] For the assessment of alcohol intake, the Alcohol Use Disorders Identification Test-Consumption (AUDIT) tool, developed by WHO, or its shorter version AUDIT-C, which includes the first three questions of the full questionnaire, has been validated and translated into multiple languages.[61] Biomarkers for alcohol consumption, such as carbohydrate deficient transferrin (CDT)[62] and phosphatidylethanol[63] can be of value. Phosphatidylethanol is excellent for confirming low alcohol intake and abstinence with high accuracy.[64] However, both phosphatidylethanol and CDT are less accurate for quantifying high alcohol intake,[64] making them less useful for differentiating between MetALD and ALD.

Steatohepatitis

Steatohepatitis is considered the primary driver of liver fibrosis, making the presence of steatohepatitis an inclusion criterion in the European Medicines Agency and US Food and Drug administration (FDA) guidance of designing drug trials in patients with MASLD.[65] Both agencies also recommend the histological resolution of steatohepatitis as a surrogate marker for clinical benefit in these trials on par with the improvement of liver fibrosis. The diagnosis of steatohepatitis is based on three histological features: steatosis (lipid droplets within hepatocytes), inflammation (infiltration of inflammatory cells in the liver lobules), and hepatocyte ballooning (cellular swelling). However, there is considerable intra-observer and inter-observer variation in the histological diagnosis of steatohepatitis,[66] and no non-invasive methods can accurately assess hepatocyte ballooning or lobular inflammation.[67] Therefore, the assessment of steatohepatitis is not part of the diagnostic framework for early detection of fibrosis in steatotic liver disease (figure 3), but remains mandatory for inclusion in drug trials for patients with MASLD.

Fibrosis

The presence and progression of liver fibrosis is the main predictor of liver-related events across the whole spectrum of steatotic liver disease;[12,13,47] therefore, biomarker development and testing approaches have been focusing on staging of liver fibrosis. Fibrosis severity has traditionally been staged on liver biopsy on a 5-point semiquantitative scale from 0 to 4: F0 (no fibrosis), F1 (mild fibrosis), F2 (moderate fibrosis), F3 (severe fibrosis), and F4 (cirrhosis).[41] Scores of ≥F2 denote significant fibrosis, while ≥F3 indicates advanced fibrosis. The presence of significant and most importantly advanced fibrosis is associated with liver-related morbidity and mortality.[12,13,72] Although steatotic liver disease is prevalent in up to 30% of the adult population, only a minority have advanced liver fibrosis.[3] This circumstance

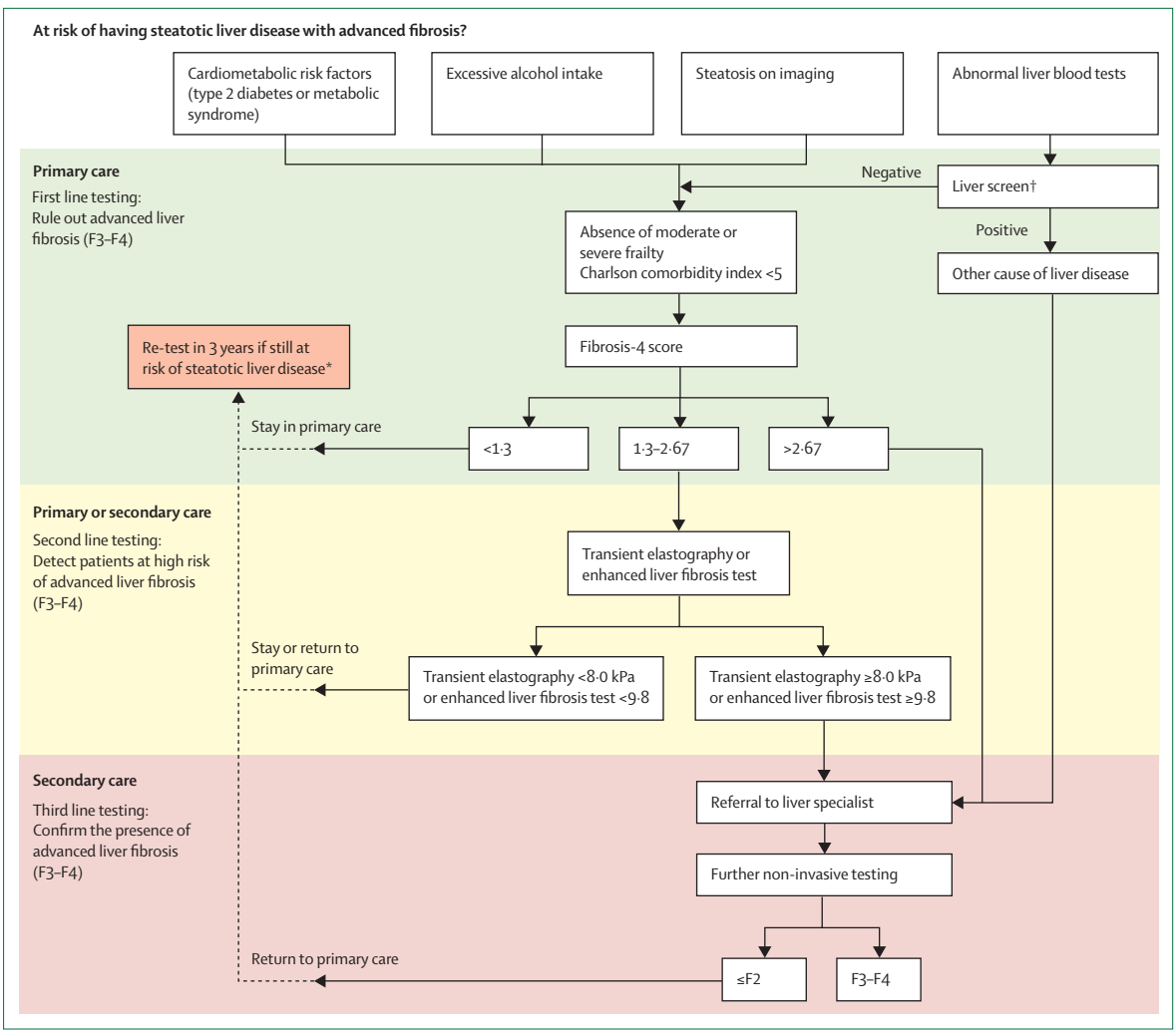
At risk of having steatotic liver disease with advanced fibrosis?
Cardiometabolic risk factors (type 2 diabetes or metabolic syndrome)
Excessive alcohol intake
Steatosis on imaging
Abnormal liver blood tests
Primary care
First line testing:
Rule out advanced liver fibrosis (F3–F4)
Negative
Liver screen†
Positive
Other cause of liver disease
Absence of moderate or severe frailty
Charlson comorbidity index <5
Fibrosis-4 score
Re-test in 3 years if still at risk of steatotic liver disease*
Stay in primary care
<1·3
1·3–2·67
>2·67
Primary or secondary care
Second line testing:
Detect patients at high risk of advanced liver fibrosis (F3–F4)
Transient elastography or enhanced liver fibrosis test
Stay or return to primary care
Transient elastography <8·0 kPa or enhanced liver fibrosis test <9·8
Transient elastography ≥8·0 kPa or enhanced liver fibrosis test ≥9·8
Secondary care
Third line testing:
Confirm the presence of advanced liver fibrosis (F3–F4)
Referral to liver specialist
Further non-invasive testing
Return to primary care
≤F2
F3–F4

Figure 3: **Diagnostic framework for early detection of advanced liver fibrosis in steatotic liver disease**
The framework is validated[68] and structured around a three-tier testing process,[69] each with its specific purpose. First-line testing uses affordable, accessible index tests (eg, Fibrosis-4) in primary care to rule out advanced liver fibrosis, emphasising a high sensitivity and negative predictive value to limit further testing. Second-line testing is conducted in primary or secondary care depending on the health-care system's structure. These more costly, specialised tests (eg, transient elastography or enhanced liver fibrosis) aim to detect patients at high risk of advanced fibrosis. Third-line testing is performed by liver specialists to confirm the presence of advanced liver fibrosis and plan a treatment strategy. Confirmation can involve further non-invasive testing or a liver biopsy, particularly in cases of discordant non-invasive test results. In this diagnostic framework, we propose ways to rationalise testing and reduce the burden for health-care systems by using the frailty and the Charlson comorbidity index to select people who would benefit most.[70] ≤F2=absence of advanced fibrosis. F3–F4=presence of advanced fibrosis.*Patients who are classified as not having advanced fibrosis should return to primary care or their already ongoing non-hepatology specialised care. Risk factors for steatotic liver disease should be managed at these levels according to standard guidelines (panel 4). If risk factors for steatotic liver disease persist, patients should be re-tested after 3 years. Due to the slow fibrosis progression in MASLD, re-testing can be omitted in patients with MASLD older than 65 years, as the 10-year risk of developing decompensated liver disease or hepatocellular carcinoma is less than 0·5% in patients with MASLD and without advanced fibrosis.[13] †Liver screen refers to the recommended investigation of an individual with prolonged abnormal liver blood tests.[71] In adults, a standard liver aetiology screen should include an abdominal ultrasound scan, hepatitis B surface antigen, hepatitis C antibody (with follow-on PCR if positive), anti-mitochondrial antibody, anti-smooth muscle antibody, antinuclear antibody, serum immunoglobulins, ceruloplasmin levels in people younger than 40 years, alpha 1-antitrypsin levels, and simultaneous serum ferritin and transferrin saturation. In this context, a negative liver screen means that no other cause for the abnormal liver blood tests has been identified other than the risk factors for steatotic liver disease. In the case of a negative liver screen, patients should be evaluated for liver fibrosis according to this diagnostic framework. A positive liver screen indicates that another cause for the abnormal liver blood tests has been found, and individuals should be referred directly to a liver specialist. Although significant fibrosis would be a reasonable target, the diagnostic accuracy of existing non-invasive tests is suboptimal and we therefore focus on advanced liver fibrosis.[59,69]

implies that most patients with steatotic liver disease can be managed for their metabolic comorbidities and excessive alcohol consumption in primary care, community centres, and obesity and endocrinology clinics, and will not require dedicated follow-up by a hepatologist. Furthermore, there are important implications for identification of liver fibrosis, as there should be a stepwise approach using non-invasive tests for case finding of liver fibrosis with the first-tier testing performed in primary care settings (figure 3).

A range of biomarkers with varying strengths are commonly used for case-finding of liver fibrosis (table 1).

For first-tier testing, Fibrosis-4 (FIB-4) is the most used biomarker and recommended in leading guidelines.[69,78] FIB-4 is inexpensive, easy to calculate, and works as a traffic light in terms of risk stratification. A value of less than 1·3 has a high sensitivity and negative predictive value for advanced fibrosis and is associated with a very low risk of liver-related events. FIB-4 can therefore serve to rule out significant liver fibrosis and the need for referral and further fibrosis testing. Patients with a FIB-4 of higher than 1·3 should undergo further fibrosis testing with either a serum biomarker or an elastography method, usually transient elastography.[69] The Enhanced Liver Fibrosis test is a proprietary serum biomarker that has been validated for both MASLD and ALD.[73,79] A cut-off score of 9·8 can be used to guide secondary care referrals, while a cut-off of 11·3 is indicative of cirrhosis.[80] Values of vibration controlled transient elastography of 8 and 12 kPa have 90% sensitivity and specificity, respectively, for advanced fibrosis.[81] Due to the low pre-test probability of advanced fibrosis in unselected populations, a two-tier testing system will still produce over 40% of false positive results. The use of concordant independent fibrosis tests is therefore recommended to reduce the need for confirmatory liver biopsies,[82] which is particularly important for the selection of patients with MASLD and fibrosis who would benefit from pharmacotherapy. Liver biopsy might be required in patients with discordant results of non-invasive fibrosis assessment or in diagnostic uncertainty.

Guidelines are moving from testing for fibrosis in patients with an established diagnosis of steatotic liver disease to testing in patients with risk factors for steatotic liver disease, such as those with type 2 diabetes, obesity, or excessive alcohol consumption.[69,78,83] Such strategies have important resource implications for widespread implementation and would require a substantial increase in the biomarker testing capacity outside hepatology

	Components	Setting	Cut-offs	Diagnostic accuracy for advanced fibrosis (AUROC)	Prognostic Discrimination (hazard ratio)	Comments
LiverRisk score	Age, sex, glucose, cholesterol, AST, ALT, GGT, and platelet count	First line testing	6, 10, 15	NA	471 for the high-risk group	Derived in the general population
Fibrosis-4 test	Age, AST, ALT, and platelet count	First line testing	<1·3, >2·67	0·76	18·76 for high cut-off	Not useful in people younger than 35 years; age adjusted cut-off proposed for those older than 65 years
Non-alcoholic fatty liver disease fibrosis score	Age, BMI, AST, ALT, type 2 diabetes, platelet count, and albumin	First line testing	<–1·5, >0·67	0·73	18·51 for high cut-off	Only validated in metabolic dysfunction-associated steatotic liver disease; performs worse than Fibrosis-4 test
Enhanced liver fibrosis test	Tissue inhibitor of metalloproteinases 1, aminoterminal propeptide of type III procollagen, and hyaluronic acid	Second line testing	9·8	0·83	16·94 for >10·5 in alcohol-related liver disease	Also increased in extra-hepatic fibrotic conditions; influenced by age
ADAPT	Pro-C3 (N-terminal type III collagen propeptide), age, diabetes, and platelet count	Second line testing	6·32	0·85	NA	Less well validated in steatotic liver disease
Transient elastography	Imaging	Second line testing	<8 KPa, >12 KPa	0·85	HR 10·65 for >20 KPa	Needs to be performed in a fasting state; requires a trained operator
2D shear wave elastography	Imaging	Second line testing	<8 KPa, >12 KPa	0·85	21·6 for >16·4 KPa in alcohol-related liver disease	Needs to be performed in a fasting state; requires a trained operator
Magnetic resonance elastography	Imaging	Second or third line testing	3·5 KPa	0·92	NA	Not widely available

The diagnostic accuracy and prognostic discrimination data presented derive from published studies.[12,70,71,73-77] The diagnostic accuracy data refer to the diagnosis of advanced fibrosis. The prognostic discrimination refers to liver-related mortality. When dual cut-offs are presented, the low cut-off is used to rule out and the high cut-off to diagnose advanced fibrosis. Values for cut-offs, diagnostic accuracy, and prognostic discrimination are based on data from meta-analyses or studies with validation. Diagnostic accuracy refers to fibrosis stage ≥F3 (advanced fibrosis). Prognostic discrimination refers to the development of liver-related events. ALT=alanine aminotransferase. AST=aspartate aminotransferase. AUROC=area under the receiver operating curve. GGT=gamma glutamyl transpeptidase. NA=not applicable.

Table 1: **The commonest biomarkers for fibrosis assessment and prognostication in steatotic liver disease**

settings. Implementation of the guidelines will require the rationalisation of the tested population, with the exclusion from testing of individuals with considerable comorbidities in which the diagnosis of advanced fibrosis would not change prognosis. Ongoing studies will provide more data on the validity of such approaches.[84]

Prognostication, monitoring, and clinical follow-up

Patients with steatotic liver disease have excess non-liver-related mortality, which argues for the need of multidisciplinary models of care. In unselected patients with MASLD, cardiovascular disease is the main cause of death, followed by non-liver related cancers.[85] The risk of cardiovascular disease increases with worsening fibrosis severity.[86] Among people who consume alcohol, there is an almost 20% excess risk of death from cardiovascular disease, cancer, non-medical causes, and all-cause mortality for every 100 g per week higher alcohol intake.[87]

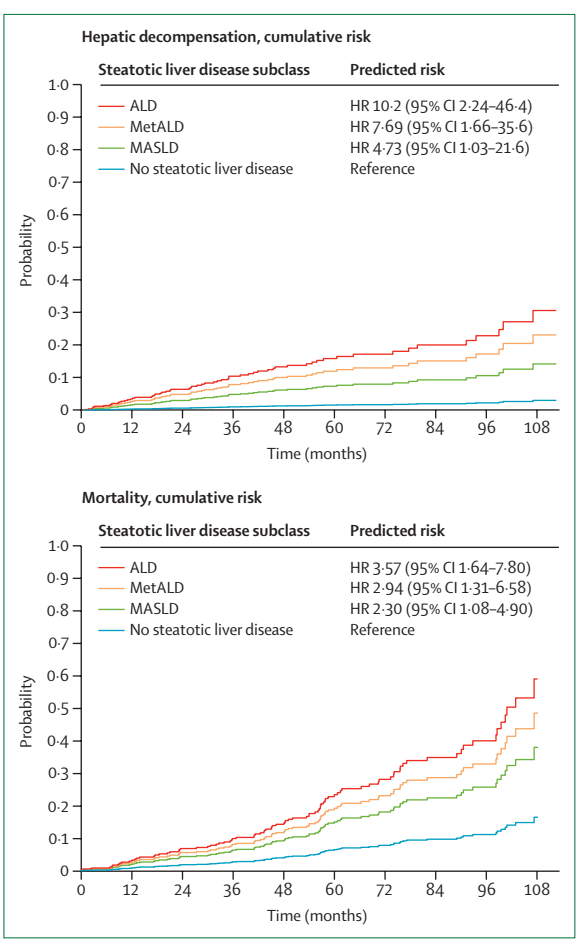

Figure 4: **Predicted cumulative hazard risk curves showing distinct prognoses for the common subclasses of steatotic liver disease**
Models are adjusted for age, sex, and liver stiffness and based on data from the study by Israelsen and colleagues.[47] ALD=alcohol-related liver disease. HR=hazard ratio. MASLD=metabolic dysfunction-associated steatotic liver disease. MetALD=metabolic dysfunction and alcohol-related liver disease.

Disregarding the uncommon instances of ALD without CMRFs, steatotic liver disease is effectively a spectrum influenced by alcohol consumption, transitioning between MASLD, MetALD, and ALD with increasing worsening of prognosis.[88] Looking at the risk of hepatic decompensation, the subclasses show a stepwise increase going from MASLD, to MetALD, to ALD, with hazard ratios escalating from 5, to 8, and then to 10, compared with patients without steatotic liver disease (figure 4).[47] In a prospective study of 1773 adults with MASLD, the incidence of liver-related events was 0·99 per 100 person years for F3 grade fibrosis and 2·69 for patients with F4 grade.[13] Conversely, in a prospective cohort of 462 patients with ALD, 18% developed a liver-related event after a median of 18 months.[12] Although studies suggest that the prognosis for MetALD falls between MASLD and ALD,[44,89–91] data are still scarce, and the prognosis could vary across populations depending on how individuals with MetALD present in terms of socioeconomic status and the severity of cardiovascular comorbidity.[92]

Historically, MASLD and ALD have been regarded as distinct conditions, but in clinical practice many individuals have risk factors for both conditions, and this overlap adversely affects the prognosis.[39,40] Indeed, observational studies suggest a supra-additive interaction of metabolic comorbidities and alcohol intake in terms of liver-related events.[93] In a cohort of over 50 000 patients with diabetes, the attributable fraction of alcohol to the liver burden was 55%.[94] Variations in alcohol intake[47] and the level of control of metabolic comorbidities[95] have a considerable effect on liver disease progression in steatotic liver disease. The profound interaction between alcohol, type 2 diabetes, and obesity suggests that patients harbouring multiple risk factors require more aggressive assessment, monitoring, and treatment.[93,96,97] The presence of genetic factors, such as single nucleotide polymorphisms in *PNPLA3*, *TM6SF2*, *MBOAT7*, and *HSD17B13*, can influence the progression of fibrosis and the development of hepatocellular carcinoma.[98] The combination of these polymorphisms in polygenic risk scores in addition with clinical characteristics might have the potential to offer personalised monitoring strategies in the near future.[99] Figure 5 summarises multiple factors that need to be taken into account when assessing patients with steatotic liver disease in specialised liver units.

The amount of alcohol consumption strongly correlates with the risk of disease progression and prognosis at any stage of steatotic liver disease.[12,47,107,108] A study involving 461 individuals with a history of alcohol consumption and early-stage ALD showed a 15% lower risk of liver-related events after 5 years among those who ceased drinking.[12] Similar findings were observed in advanced stages of ALD with decompensated disease.[107] Changes in alcohol intake can also strongly affect hypertension and

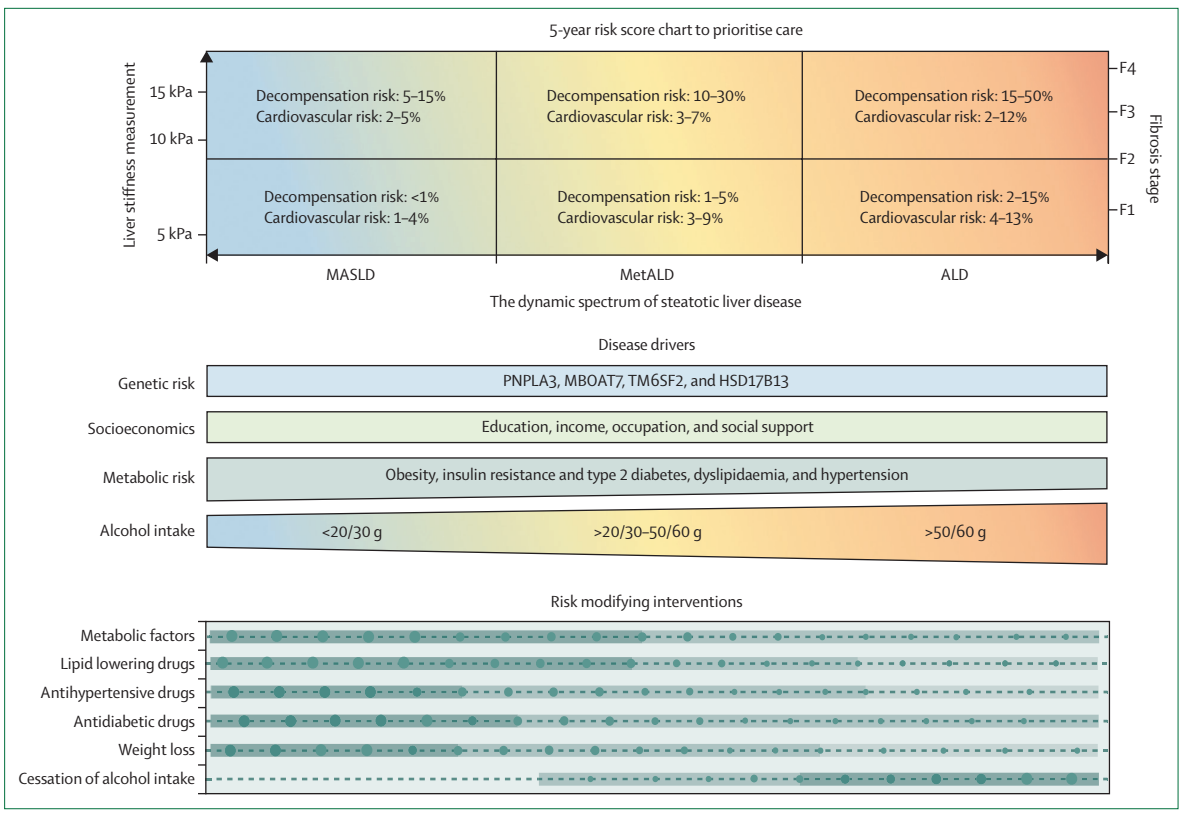

Figure 5: **How to evaluate patients with steatotic liver disease in specialised liver units**
Based on the primary evaluation of a patient with steatotic liver disease, the 5-year risk of progression to clinically significant hepatic and cardiovascular disease can be estimated. This estimation should be considered when planning follow-up care for each patient with steatotic liver disease in alignment with current guidelines.[67,76–78] The specified values for liver stiffness measurement refer to measurements conducted with FibroScan. The figure is inspired by the figure by Israelsen and colleagues[100] with an expansion on risk modifying interventions across the spectrum of steatotic liver disease and data on cardiovascular risk for patients with steatotic liver disease.[31] Risk estimates for hepatic decompensation and cardiovascular risk are based on published studies.[12,13,47,101–106] ALD=alcohol-related liver disease. F1=mild fibrosis. F2=moderate fibrosis. F3=severe fibrosis. F4=cirrhosis. MASLD=metabolic dysfunction-associated steatotic liver disease. MetALD=metabolic dysfunction and alcohol-related liver disease.

dyslipidaemia, necessitating reassessment when patients alter their alcohol intake.

The intensity and setting (primary *vs* secondary care) of monitoring depends on the burden of cardiometabolic comorbidities and the presence and severity of liver fibrosis. Patients with minimal or no fibrosis can be managed by alcohol services in the presence of alcohol-use disorder and primary care or endocrinology settings with a focus on cardiometabolic risk in MASLD. If there is significant liver fibrosis, patients should also be managed by a hepatologist with the aim of monitoring liver disease progression, treating liver fibrosis, and screening for complications of cirrhosis. Non-invasive fibrosis tests can also be used for risk stratification and longitudinal monitoring.[69] These tests including FIB-4, transient elastography, and ELF also provide prognostic information in steatotic liver disease.[12,74] An FIB-4 score lower than 1·3 is associated with very low risk of liver-related events. Scores specifically developed to predict the risk of liver-related events are emerging to reduce the false positive rates associated with use of current diagnostic fibrosis biomarkers.[109–111] The LiverRisk score was recently developed in a general population cohort and independently validated against clinical outcomes and can stratify people across four risk categories for predicting the liver-related prognosis.[75] Similarly, the MAF-5 score, comprising waist circumference, BMI, diabetes, aspartate aminotransferase, and platelets, was developed in the general population and validated in multiple cohorts, and also predicts liver-related prognosis.[112] The Baveno rule-of-5 (ie, elastography values of >5, >10, >15, and >20 KPa) can be used to stratify patients at different risks of hepatic decompenstaion.[113] Changes in the results of non-invasive tests can be used for monitoring the disease as they indicate improved or worsening prognosis.[114,115]

Current management of steatotic liver disease

The steatotic liver disease concept subsequently implies that if multiple risk factors for steatosis are present, management of all these causes is required. However, for patients with newly diagnosed steatotic liver disease, initiating the treatment for all risk factors at once can be extensive and overwhelming. Therefore, it is essential to conduct a risk assessment to prioritise care, bearing in

mind that the goal of any treatment is to reach a clinically meaningful benefit (figure 5). In case of a combination of both alcohol and metabolic dysfunction as causes, it can be argued that if a combined approach is not feasible, priority is given to manage the excessive alcohol intake and to tackle the cardiometabolic disease drivers as a second step. Patients with steatotic liver disease who are identified with significant fibrosis should be offered more intensive liver-directed management by a hepatologist. To date, for MASLD, these benefits have been defined by histological response, both for practice guideline recommendations and for drug development: resolution of MASH and improvement of fibrosis.[65] Although plausible, whether these surrogates truly result in better outcomes still needs to be validated as only one study so far could show, in a cohort of patients with cirrhosis, that fibrosis regression reduces the risk of liver-related events.[116]

Body composition and weight loss

The cornerstone of treating the metabolic dysfunction associated component of steatotic liver disease, whether isolated or combined with other risk factors for chronic liver disease, is the control of the CMRFs as drivers of disease (figure 5).[95,117] As adipose tissue dysfunction is a crucial aetiological factor, weight loss resulting in improved adipose tissue function, improves liver condition. Studies with paired biopsy have shown that patients need 7–10% of bodyweight loss to have fibrosis improvement.[117] It is currently unclear whether the strategy to obtain weight (eg, caloric restriction and increased physical activity, bariatric or metabolic surgery, or weight lowering treatments) adds to the amount of weight loss. Weight lowering drugs (eg, glucagon-like protein 1 [GLP1] receptor agonists) have been best documented, with semaglutide showing an effect size (for a subcutaneous dose of 0·4 mg) of 42% over placebo in terms of MASH resolution in patients without cirrhosis in a phase 2 trial.[118] However, 18 months of treatment with semaglutide did not result in fibrosis regression, illustrating that a pure metabolic approach tackling the extrahepatic disease drivers is not enough for fibrosis regression in such a time period. Furthermore, in patients with MASH cirrhosis, despite weight loss and cardiometabolic improvement, there was no benefit in terms of fibrosis improvement.[119] However, reports from post-bariatric surgery series of up to 5 years do show the possibility of fibrosis improvement by weight loss,[120] but long-term maintenance of the weight loss seems necessary and does not occur in all patients.[121]

Dual and triple GLP1 receptor agonists, glucagon receptor, and glucose-dependent insulinotropic polypeptide are all being tested as specific MASH treatments and some of them are already approved for diabetes or obesity. Data on non-invasive markers, in particular liver steatosis content by MRI-proton density fat fraction, show promising results but data on histology have not been published yet and whether they have a benefit beyond the induced weight loss remains to be established,[122] which also holds true for sodium glucose co-transporter 2-inhibitors (SGLT2i).[122,123] Some guidelines recommend that these drugs can be used for MASH in individuals meeting the criteria of the approved indications, and an associated benefit on MASH is likely,[83] but the effect on long-term outcomes still needs to be established.

Pioglitazone, a peroxisome proliferator-activated receptor (PPAR)-γ agonist, has phase 2 and 4 data showing histological benefit on NASH resolution (but not fibrosis regression) and can also be used within its approved indication.[124,125] Pioglitazone improves overall atherosclerotic cardiovascular events and outcomes, but caution is warranted in patients with reduced cardiac function (New York Heart Association class I and II heart failure) and contraindicated in class III or IV heart failure.[126]

Other CMRF treatments

Other drugs used to treat CMRFs also might have some benefit for the treatment of MASLD. Statins might slow down disease evolution towards decompensation and hepatocellular carcinoma, probably due to the vascular effect, which is considered an important pathophysiological mechanism for MASH disease progression.[127,128] Aspirin and other anti-platelet treatment could have the same beneficial effect.[129] Physicians should therefore be informed and encouraged to prescribe statins and aspirin for steatotic liver disease when indicated for primary or secondary prophylaxis of cardiovascular events, as these could have additional benefits of preventing liver disease progression and development of hepatocellular carcinoma.[130,131] Besides a potential beneficial role of angiotensin-converting enzyme inhibitors[132,133] there are little or no data on the potential liver benefit of antihypertensive treatment.

Licensed anti-MASH treatments

The thyroid hormone receptor-β agonist resmetirom has shown beneficial effects on both MASH resolution (in the 100 mg group 29·9% had MASH resolution *vs* 9·7% in the placebo group, risk difference to placebo 20·7%, 95% CI 15·3–26·2, p<0·001) and fibrosis regression (in the 100 mg group 25·9% had fibrosis regression *vs* 14·2% in the placebo group, risk difference to placebo 11·8%, 95% CI 6·4–17·2, p<0·001) in a phase 3 trial[134] and is the first drug to have obtained FDA accelerated approval (March, 2024) for the treatment of patients with MASH and fibrosis consistent with F2–F3 score, therefore, could be brought to the market. Hence, it is the first drug for MASH as a formal indication. No other drugs are currently licensed for indication of MASH.

Alcohol

Any reduction in alcohol consumption leads to improved outcomes and should be actively pursued. Behavioural interventions and relapse prevention medications, either alone or in combination, represent the first line treatment.

Screening for alcohol intake, providing information, and referring patients to local addiction services are imperative. Brief motivational interventions, feasible for most clinicians, have been shown to reduce alcohol consumption in a meta-analysis (mean difference –20 g per week, 95% CI, –29 to –12).[135,136] Pharmacotherapy should be considered for all people with harmful alcohol consumption who cannot reduce intake with behavioural approaches. Drugs include acamprosate that reduce craving and have shown efficacy in supporting abstinence compared with placebo in a meta-analysis (risk reduction 0·83, 95% CI 0·77–0·88), and naltrexone for preventing relapse (risk reduction 0·83, 95% CI 0·75–0·91).[137,138] Disulfiram is not recommended due to the risk of liver toxicity and restricted efficacy.

A subset of patients with steatotic liver disease might present with addiction to either food or alcohol, necessitating specialised treatments tailored to address conditions, such as alcohol-use disorder, alcohol dependence, or eating disorders. However, most patients can considerably mitigate their behaviour-related risk factors with interventions readily implemented in most clinical settings.[139] Recent research involving nearly 5000 individuals revealed that providing specific information regarding liver damage coupled with appropriate advice led to notable improvements in behaviours related to alcohol consumption (excessive drinking reduced from 46% to 32%), 35% improved diet, 13% lost bodyweight, and 22% increased exercise.[140]

Holistic and multidisciplinary management

Management of steatotic liver disease needs a holistic and multidisciplinary approach to adequately address all risk factors and associated conditions.[141] The practical implementation is still maturing, and several models of care can be envisioned, tailored to local resources and organisation of health care systems.[142] Depending on the health-care system, the management of cardiometabolic risk factors typically takes place with primary care physicians, but it can also occur in clinics specialising in the management of cardiometabolic risk factors and alcohol services. Such a multidisciplinary approach has, in an observational study, shown that patients with MASLD benefit from lifestyle advice, signposting to weight loss services, and pharmacological treatment of diabetes and cardiovascular risk factors, which improved both cardiovascular and liver-related parameters.[143] Another example from UK community alcohol services showed that the introduction of liver stiffness assessment for patients with excessive alcohol consumption improved their engagement and retention and also suggested that it could support the reduction in alcohol intake.[139]

Multidisciplinary care models should become the standard of care to tackle the multiple comorbidities of steatotic liver disease and should be combined with preventive measures at a societal and individual level (panel 4).[144,145]

Drug development across the steatotic liver disease spectrum

New therapeutic modalities for steatotic liver disease are developed for the underlying aetiologies, mainly referring to MASLD[146] or ALD. MetALD represents a novel target population for drug development, with a rapidly growing interest from drug developers in this specific population that target both causes cardiometabolic and alcohol-related drivers.[146]

Novel treatments for MASLD focus mainly on endoscopic procedures and on drugs. Therapeutic targets can conceptually be separated into primarily metabolic pathways, mechanisms of cell stress and apoptosis, inflammation, fibrogenesis, and genetic targets,[124,147] with some of them being common with MetALD and ALD (figure 6). Many approaches have combined effects directly on several targets.

Panel 4: **Standard treatments for cardiometabolic risk factors and alcohol intake**

Overweight or obesity
The target is at least 7–10% weight loss with a staged approach. Treatment should start with counselling for lifestyle modification, diet, and exercise. GLP1 receptor agonists or dual agonists or bariatric surgery should be considered if lifestyle modifications are unsuccessful in patients who fulfil the criteria for these treatments (eg, weight lowering drugs usually BMI >30 kg/m^2 or >35 kg/m^2 with comorbidities, and surgery BMI >40 kg/m^2 or >35 kg/m^2 and comorbidities).

Type 2 diabetes
Preference for drugs that might affect liver inflammation or liver fibrosis, such as GLP1 receptor agonists, SGLT2 inhibitors, or pioglitazone. The choice depends on BMI and comorbidities.

Hyperlipidaemia
Patients can be offered statins for primary or secondary prevention of cardiovascular events according to guidelines and treatment thresholds.

Hypertension
Start patients on treatment if blood pressure above 140/90 mm Hg or 130/80 mm Hg in patients with type 2 diabetes who are at higher cardiovascular risk. There is no preference for a particular drug class.

Smoking
Smoking cessation should be encouraged and pharmacotherapy can be offered if required.

Sleep apnoea
Evaluate patients for sleep apnoea and continuous positive airway pressure can be offered if required.

Alcohol intake
Any reduction at any stage of disease improves outcomes. Patients with advanced fibrosis or cirrhosis should be advised to complete abstinence. Binge drinking should be avoided. A combination of behavioural motivational modalities and relapse prevention medication, such as acamprosate or naltrexone is recommended. Individuals with alcohol-use disorder should be referred to specialised community programmes.

Many drugs targeting MASH are under investigation (table 2). Resmetirom is now licensed by the FDA for patients with MASH and moderate (F2) or severe (F3) fibrosis, but not yet in cirrhosis, for which the phase 3 trial is ongoing. The other drugs tested in phase 3 trials are the GLP-1 receptor agonist semaglutide, the panPPAR agonist lanifibranor, the fibroblast growth factor-21 (FGF21) analogues efruxifermin and pegozafermin, the fatty acid synthase inhibitor denifanstat, and survodutide, a dual agonist of the glucagon and GLP-1 receptors. The phase 2b trial of lanifibranor showed an effect size of 19% (risk ratio [RR] 1·7, 95% CI 1·2–2·5) for fibrosis regression and 27% (RR 2·2, 95% CI 1·5–3·3) for MASH resolution after 6 months of treatment.[149] There were no major safety issues and the drug was generally well tolerated. Some weight gain was noted attributable most probably to PPAR-γ activity. Two studies with FGF21 analogues have shown positive results in phase 2 trials. The highest doses of pegozafermin showed an effect size of 20% (RR 4·19, 95% CI 1·47–11·93) for fibrosis regression and 24% (RR 15·55, 95% CI 2·11–114·86) for MASH resolution after 6 months of treatment.[150] Efruxifermin showed an effect size of 21% (RR 2·2, 95%CI 1·0–5·0, p=0·036) for fibrosis regression and 61% (RR 5·2, 95% CI 2·4–11·1, p<0·001) for MASH resolution after 24 weeks of treatment.[151] However, the effect size of the trials cannot be compared due to substantial differences in trial design and primary analyses presented. Side-effects were mainly gastrointestinal in nature, sometimes leading to treatment discontinuation. Denifanstat showed an effect size of 16% (RR 2·14, 95% CI 1·06–4·35) for fibrosis regression, and 15% (RR 2·36, 95% CI 1·05–5·30) for MASH resolution after 52 weeks of treatment.[152] Side effects were mainly gastrointestinal and dermatological. Survodutide showed an effect size on fibrosis regression of 13% (RR 1·58, 95% CI 0·99–2·51) and MASH resolution of 37% (RR 3·61, 95% CI 2·02–6·45), with no clear dose-response relationship. Side effects were mainly gastrointestinal.[153]

A plethora of drugs with many different modes of action are currently under investigation, including those with genetic targets—eg, an siRNA lowering the mRNA expression of *PNPLA3* and an siRNA directly reducing hepatic hydroxysteroid 17β dehydrogenase 13 (*HSD17B13*) expression.[124] The gut–liver axis can be targeted at several

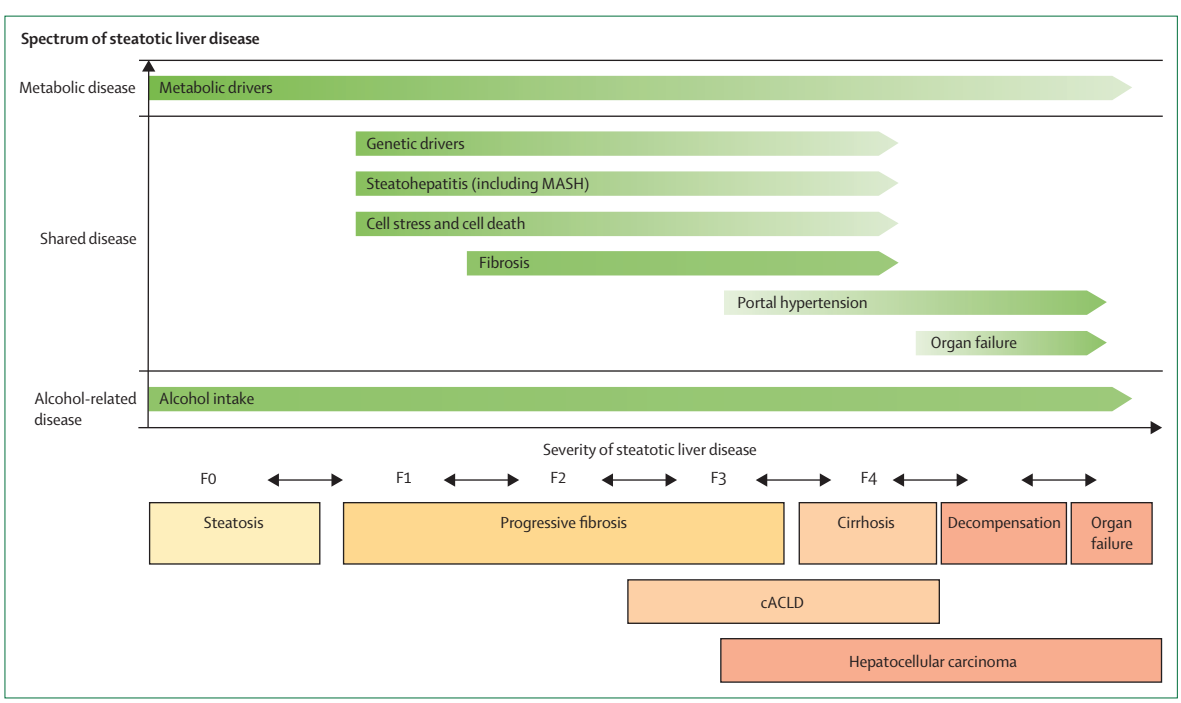

Figure 6: **Drug targets along the spectrum and severity of steatotic liver disease**
Along the spectrum and severity of steatotic liver disease, the role and target of different factors contribute to disease progression. Alcohol-related damage is a driver often at all severity stages of steatotic liver disease. For metabolic disease (ie, MASLD), metabolic drivers play a dominant role. Across the spectrum of steatotic liver disease, metabolic drivers and alcohol lead to steatosis and steatohepatitis. Steatohepatitis has its own intrahepatic mechanisms and drives fibrogenesis and progression towards advanced chronic liver disease and portal hypertension, and ultimately organ failure.[10] Although, in more advanced disease stages and even in cirrhosis and portal hypertension, metabolic factors and intrahepatic mechanisms of cell damage and inflammation, cell stress, and cell death might still play a role, even though they tend to diminish and disappear, and portal hypertension becomes a predominant driver of disease. The green arrows illustrate where drug targets are relevant along the spectrum and the severity of steatotic liver disease. Less colour intensity of the arrows symbolises less relevance of a given drug target. Drugs targeting metabolic drivers or intrahepatic mechanisms are more relevant at earlier time points in the disease severity and are less likely to be efficacious in the advanced stages, where drugs tackling fibrogenesis and the (vascular) mechanisms underlying portal hypertension are could be of clinical benefit.[148] Changing lifestyle is crucial at all stages and might be supported by pharmacotherapy in the context of addiction management. cACLD=compensated advanced chronic liver disease. F0=no fibrosis. F1=mild fibrosis. F2=moderate fibrosis. F3=severe fibrosis. F4=cirrhosis. MASH=metabolic dysfunction-associated steatohepatitis.

	Mode of action	Estimated patient enrolment	Fibrosis stage	Study duration	Endpoints	Sponsor	Clinical trial number
Semaglutide	GLP-1 receptor agonist	1200	F2–F3	Up to 5 years, interim analysis at 72 weeks	Clinical outcomes; histological for interim analysis	Novo Nordisk	NCT04822181
Resmetirom*	THRb agonist	1759 (actual)	F2–F3	Up to 5 years, interim analysis at 52 weeks	Clinical outcomes; histological for interim analysis	Madrigal Pharmaceuticals	NCT03900429
Resmetirom	THRb agonist	700	F4	Up to 3 years	Clinical outcomes	Madrigal Pharmaceuticals	NCT05500222
Lanifibranor	Pan-PPAR agonist	1000	F2–F3	72 weeks, with a further 48 week follow up for safety	Histological	Inventiva	NCT04849728
Pegozafermin	FGF21 analogue	1050	F2–F3	88 weeks, interim analysis at 52 weeks	Clinical outcomes; histological for interim analysis	89Bio	NCT06318169
Efruxifermin	FGF21 analogue	1000	F2–F3	Unknown, interim analysis at 52 weeks	Clinical outcomes; histological for interim analysis	Akero Therapeutics	NCT06215716
Efruxifermin	FGF21 analogue	600	MASLD or MASH based on biopsy or non-invasive testing	52 weeks	Safety and tolerability	Akero Therapeutics	NCT06161571
Denifanstat	FASN inhibitor	1260	F2–F3	Up to 4·5 years, interim analysis at 52 weeks	Clinical outcomes; histological for interim analysis	Sagimet	NCT06594523
Survodutide	Glucagon receptor and GLP-1 receptor agonist (dual)	1800	F2–F3	Up to 7 years, interim analysis at 52 weeks	Clinical outcomes; histological for interim analysis	Boehringer Ingelheim	NCT06632444
Survodutide	Glucagon receptor and GLP-1 receptor agonist (dual)	1590	F4	Up to 4 years	Combined clinical and biochemical outcome	Boehringer Ingelheim	NCT06632457

F2=moderate fibrosis. F3=severe fibrosis. F4=cirrhosis. FASN=fatty acid synthase. FGF21=fibroblast growth factor 21. GLP-1=glucagon-like peptide 1. MASH=metabolic dysfunction-associated steatohepatitis. MASLD=metabolic dysfunction-associated steatotic liver disease. PPAR=peroxisome proliferator-activated receptor. THRb=thyroid hormone receptor b.*Results have been published.[134]

Table 2: **Current phase 3 drug trials in MASLD**

steps preventing translocation of microbial products from gut to the liver to reduce liver inflammation and fibrosis progression—eg, a gut-specific antibiotic, rifaximin-α that is considered to improve the gut barrier might reduce progression of liver fibrosis in patients with ALD.[154]

Many drug trials primarily involve patients without cirrhosis, a trend that arose from repeated failures in trials involving patients with cirrhosis. Such failures might stem from the disparity between drug targets and the varied disease drivers spanning the disease severity (figure 6). The prevailing model for drug approval necessitates trials in patients with cirrhosis with clinical endpoints, as conducting outcome studies at earlier stages is challenging due to the slow and unpredictable progression of disease. Acknowledging this challenge, several phase 3 compounds are concurrently undergoing separate trials in patients with cirrhosis. Non-invasive disease markers have been insufficiently validated as substitutes for histology or clinical outcomes to be accepted by the regulatory authorities for both accelerated and conditional and final approvals. Nevertheless, resmetirom secured FDA approval without explicitly necessitating a liver biopsy, suggesting potential shifts in regulatory positions.

Patients with MetALD represent a new important target group for clinical trials, as they have previously been excluded from MASH trials and as the cardiometabolic disease drivers have largely been neglected in ALD. Furthermore, there is the substantial overlap in pathophysiological, behavioural, metabolic, and genetic risk factors among MASH, MetALD, and ALD (figures 5 and 6), presenting a promising opportunity to evaluate numerous drugs currently in development for MASH in patients with MetALD and ALD.[100,146] Preclinical evidence indicates that GLP1 analogues and the hormone FGF21 can mitigate alcohol consumption via central neurotransmission pathways.[155,156] Clinical observations further suggest that FGF21 attenuated alcohol consumption in individuals with steatotic liver disease.[157] Semaglutide and tirzepatide have been shown to reduce the intake of alcohol additionally to promoting weight loss in people with obesity,[158] and are potentially attractive in MetALD patients.

Challenges and controversies

The evolving landscape of liver disease and the implementation of the steatotic liver disease nomenclature as a spectrum from MASLD and MASH to ALD, presents a complex array of challenges and potential controversies that should be addressed going forward. This shift in terminology is not just semantic; it reflects a deeper understanding of the multifactorial nature of liver disease. However, the change in terminology also introduces several uncertainties and research questions.

The criteria for alcohol consumption crucially need specificity for defining the timeframe for current and historical alcohol consumption to ensure correct subclassification of steatotic liver disease.[47] Determining when alcohol ceases to be a primary disease driver is essential, as it influences the transition between subclasses, which is particularly important in clinical trials where accurate classification affects both treatment strategies and outcome assessment. Moreover, the reliability of self-reported alcohol consumption is problematic due to the inaccuracies imposing a high risk of misclassification.[21,22] While biomarkers such as phosphatidylethanol and CDT can rule out alcohol intake, they are less effective in quantifying alcohol intake needed for steatotic liver disease subclassifcation.[62,63] Furthermore, the fluctuating nature of alcohol consumption over time adds another diagnostic challenge if steatosis is absent at the time of liver assessment. Approximately 40% of individuals show no signs of liver steatosis yet they might be at high risk of hepatic decompensation,[159] raising the question of which fibrosis thresholds should be used.

Since the introduction of the steatotic liver disease nomenclature, studies have shown that almost all individuals with a current excessive alcohol consumption also have CMRFs. In the NHANES cohort, 0·08% (95% CI 0·04–0·22) presented with ALD without CMRFs.[45] In a Danish cohort of individuals with a history of excessive alcohol consumption, only one (0·2%) of 446 individuals presented with ALD and without CMRF,[47] which shows that excessive alcohol consumption is closely associated with CMRFs, indicating that ALD without a CMRF is a subgroup that will rarely be seen.

The importance of the individual CMRF is also contentious. While conditions like type 2 diabetes and obesity are strongly associated with risk of liver-related mortality, other factors such as hypertension and dyslipidaemia are less associated. Yet, according to the steatotic liver disease criteria, each CMRF has equal weight which (the fact that they have equal weight) might not accurately reflect differences in their relative importance.

Monitoring treatment responses in clinical practice, particularly using non-invasive tests, is crucial to minimise the need for liver biopsies. This approach could enhance patient comfort and reduce health-care costs. Resmetirom, a drug for treatment of MASLD, recently secured FDA approval without explicitly necessitating a liver biopsy, suggesting potential shifts in regulatory positions.

Additionally, screening asymptomatic individuals with risk factors for liver fibrosis presents dilemmas about whom to test, the frequency of testing, and testing methods.[160] Lastly, the patient journey through the health-care system from home to primary care, to secondary care, and back to managing a chronic disease, is a crucial aspect. The role of self-monitoring and artificial intelligence tools to support clinical decision making in managing liver disease is an emerging field that promises to revolutionise patient care. While the steatotic liver disease nomenclature and diagnostic framework reflect a more nuanced understanding of liver disease, it also presents several new questions and challenges that necessitate careful consideration, consensus-building, and ongoing research.

Conclusion

There is a growing focus on advancing liver health with awareness and policy measures led by the European Association for the Study of the Liver, the American Association for the Study of Liver Disease, the *Lancet*, and WHO.[7,161,162] The overall aim is to combat steatotic liver disease with prevention and early detection and to inform policy measures to mitigate the structural determinants of poor liver health. Therefore, steatotic liver disease should be included as part of the WHO programme on fighting non-communicable diseases.[24,161,162]

A key aspect for improving global liver health will be to change the dialogue around liver diseases to reduce stigma by shifting the narrative and adopting terminology that more accurately represents their multifactorial nature, recognising that factors beyond CMRF and alcohol contribute to steatotic liver disease, and promoting more open discussions about this.[30] Furthermore, there is the need to foster a deeper understanding of steatotic liver disease among health-care professionals, patients, and the broader public.[145] On a structural level, there is a need for a unified global effort to integrate liver health into broader health policy frameworks, including prevention and enhancing early diagnosis and treatment access.[24] Such structural improvements should aim to address not only liver health, but also related metabolic and alcohol-use disorders as part of a comprehensive approach to reduce non-communicable diseases on a broader scale.

Contributors

All authors contributed equally to both the writing and critical review of the Seminar, and have given their approval for the final version to be submitted.

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